REMARKS

Claims 1-21, 31-48 and 53 are pending. Claims 1-21, 31-48, and 53 stand rejected. In this response, Applicants have presently amended claims 1, 31, and 53. Applicants also resubmit herewith a Declaration of H. Greg Thomas under 37 C.F.R. § 1.132. This Declaration was originally submitted with a response filed November 3, 2005. However, Applicants believe that Exhibits A and B may have been missing from that Declaration and so resubmit it now. In view of these amendments, the declaration, and as discussed below, it is submitted that the application is now in condition for allowance.

Summary of the Invention of the Present Application

The invention of the present application provides a composition including the tannate salts of active pharmaceutical ingredients, such as phenylephrine and pyrilamine. This composition is prepared by a method that results in the homogeneity (i.e., a general uniformity) of the amounts of the active pharmaceutical ingredients in the composition over that found in the prior art. The method of preparing the composition involves a conversion process, including mixing a dispersing agent and tannic acid in a suitable solvent to generate a mixture, referred to as a dispersion. A solution of the active pharmaceutical ingredients, as common salts or in the free base form, is added to the dispersion to generate tannate salts of the active pharmaceutical ingredients. The tannate salts are directly processed (i.e, without any isolation or purification steps) into

suitable dosage forms, such as a suspension or tablets. The use of the dispersion prevents the clumping and aggregation of the tannate salt formed. Thus, as the tannate salts are further processed into dosage forms, the dispersion promotes the general uniformity of the amounts of active pharmaceutical ingredients. Thus, each dosage unit of the dosage form (e.g., each tablet or each 5 ml of suspension) will include an amount of the tannate salts that is generally uniform to each other dosage unit (e.g., each other tablet or 5 ml of suspension). Further, the use of free base or common salt forms of phenylephrine and pyrilamine that are processed directly into tannate salts in the composition in situ, further aids in reducing variability of the active pharmaceutical ingredients in the final product. This is because there is less variability in the free base or common salts than in the tannate salts. Thus, by starting with a commonly available salt or free base of the active pharmaceutical ingredient, which is subsequently converted and incorporated in situ as a tannate salt complex, the invention provides an efficient and reproducible method to manufacture liquid, semi-solid, or solid homogeneous products containing active ingredients as tannate salt complexes.

As a result of the method used to prepare the compositions, the problem described in the application of prior art pharmaceutical compositions that contain variable, and sometimes sub-therapeutic, levels of active pharmaceutical ingredients is ameliorated by providing a composition including a generally uniform amount of active pharmaceutical ingredients from dosage unit to dosage unit. Since the tannate salts of

phenylephrine and/or pyrilamine are generated and incorporated in situ into the dosage form during the manufacturing process, the purification and drying steps, which are generally required for the isolation of the tannate salts, are also eliminated.

Claim Rejections 35 U.S.C. § 103

Claims 1-21, 31-48, and 53 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,287,597 ("Gordziel") in view of U.S. Patent No. 5,599,846 ("Chopdekar"). Applicants respectfully disagree with the rejections. As will be discussed in greater detail below, Applicants submit that neither of these references, alone or in combination, disclose or suggest a composition that is homogeneous in its active pharmaceutical ingredients. In particular, Applicants submit that the claimed composition (as recited), produced by method of an in situ conversion of a free base or salt form of the active ingredients to tannate salts to provide a composition in an amount including a plurality of dosage units, which are homogeneous in amounts of the active ingredients from one dosage unit to the next, is completely different from the composition of Gordziel or Chopdekar or any combination thereof.

Turning to the substance of the presently amended claims: Applicants first submit that independent claims 1, 31, and 53 have each now been amended to recite that the tannate salts are combined with at least one suspending agent, or granulation, to produce a "homogeneous suspension," a "homogeneous granulation" or a "homogeneous composition," including pharmaceutically active salts wherein that

suspension, granulation, or composition includes a plurality of dosage units, and "being homogeneous in amounts of active pharmaceutical ingredients in each of the dosage units when compared with each of the other dosage units." Such a composition is not found in Gordziel or Chopdekar, as will be described in greater detail below.

Applicants further submit that independent claims 1, 31, and 53 include at least two recitations that render the amounts of active pharmaceutical ingredients homogeneous in the claimed composition, thereby distinguishing the claimed composition from the compositions disclosed in the cited art. First, the recited use of a separate dispersion (including a dispersing agent such as magnesium aluminum silicate, xanthan gum, and cellulose compounds) prevents the aggregation of the tannate salts as they precipitate out of solution, thereby enhancing the homogeneity, or uniformity, of amounts of active ingredient from dosage unit to dosage unit. Second, the conversion process begins with the free base or common salt form of the active ingredient. Such forms exhibit less variability in amounts of active pharmaceutical ingredients, as opposed to the tannate form isolated and then used in the cited references. Thus, by starting with a form having less variability in amounts of the active, the claimed composition prepared in that manner also demonstrates greater uniformity of amounts of active ingredients over the cited references, once processed in situ into the tannate salt forms. These recitations of the claims will be discussed in greater detail below.

Claims 1, 31, and 53 each recite that the process for preparing the composition involves combining a solution (which includes active pharmaceutical ingredients) to a dispersion (including a dispersing agent and tannic acid). As described above, and throughout the application, the novel process of using a dispersion aids in increasing the homogeneity (i.e., the uniformity) of the amounts of active pharmaceutical ingredients from batch to batch (and thus dosage unit to dosage unit) of the presently claimed composition, as opposed to the more variable levels of active pharmaceutical ingredients present in compositions of the cited art. And, now this homogeneity in amounts of active pharmaceutical ingredients is explicitly recited in the claims. Support for this may be found at least at page 4, lines 14-15, and page 11, lines 18-20 of the present application. The application at pages 4 and 11 describes that the presence of the dispersing agent and its use in a separate dispersion (which is not found in the cited art) prevents the clumping and aggregation of the tannate salt formed. Thus, as is described at least at page 11, lines 18-20, this method, by preventing clumping and aggregation of the tannate salt, promotes uniformity of the active pharmaceutical ingredients in the compositions formed.

Further, as recited in independent claims 1, 31, and 53, the active pharmaceutical ingredient is added in its free base or salt form. This further reduces variability and promotes uniformity of API in final product. At least, at page 3, line 14 through page 4 line 2, the application describes that one problem with present

compositions is that the presence of low active percentages of antihistamine or decongestant and the variable purity of commercially available antihistamine and decongestant tannate salts results in the stoichiometry of active free-based tannic acid in the tannate salts being different from batch to batch of compositions prepared. This results in significant dosing and processing problems during manufacturing, and results in commercially available pharmaceutical compositions that contain variables, and in some instances, subtherapeutic levels of active pharmaceutical ingredients. However, by using the free base or common salt form, as in the method of the present composition claims, the present invention reduces this variability. This, however, is not seen in the cited art. The cited art (Chopdekar and Gordziel) only includes old or conventional processes for preparing compositions including tannate salts, and thus those compositions vary in their amounts of active pharmaceutical ingredients, which is wholly different than the composition recited in the present claims.

As acknowledged by the Examiner, Gordziel only teaches old isopropanol routes of preparing compositions (including pyrilamine and phenylephrine). However, the Examiner points to Chopdekar as teaching a water route, which the Examiner suggests is the same as Applicants' presently claimed process. The Examiner therefore suggests that the compositions of Gordziel could be made by the process of Chopdekar, and that the combination thereof discloses Applicants' claimed product by process claims. Since the Examiner acknowledges that Gordziel does not recite the

same process as recited in Applicants' claims, Applicants will put a discussion of Gordziel aside for now. The Chopdekar patent does describe, in some detail, a process of preparing tannate compounds.

Chopdekar describes processes for the preparation of tannate forms, for example, of pyrilamine and/or phenylephrine, which may then be used to prepare compositions including those tannate salt forms of phenylephrine and pyrilamine. In other words, the tannate forms are obtained, isolated, and purified, and then subsequently incorporated into other compositions.

Applicants submit that the use of those pyrilamine tannate and phenylephrine tannate forms, as in Chopdekar (and Gordziel), results in compositions that exhibit greater variability of active ingredients in each batch or dosage unit of the final drug composition product as compared to the presently claimed composition prepared by the method recited in those claims. (*See* Declaration of H. Greg Thomas, submitted with Response dated November 3, 2005, paragraph 5.) In fact, the Chopdekar patent says as much itself in that the Chopdekar patent describes that the water remaining following preparation of the tannate salts must be removed by a freeze-drying step, and any further water remaining is an impurity that requires an adjustment of each dosage (*see* col. 1, line 67 through col. 2, line 2; col. 2, lines 11-13; and col. 3, lines 11-30 of the Chopdekar patent). And further, although Chopdekar may describe a product purity of 90-98% (as noted by the Examiner), that has absolutely no bearing on

whether the amounts of the actives will be homogeneous from one dosage unit to the next. As described above, Chopdekar itself states that dosages of its disclosed product may need to be adjusted. Thus, Chopdekar cannot be describing a product wherein the dosages are homogeneous. And so, the presently claimed composition is completely different from that formed by the process of the Chopdekar patent. Since it is converted in situ into the tannate form and then directly into suspension, there is no water as an impurity, and the separate dispersion promotes homogeneity of the active pharmaceutical ingredients, thereby requiring no adjustment of dosages. This is wholly unlike a composition formed by the process of the Chopdekar patent.

Applicants submit that this becomes clear when comparing the specifications of active ingredient raw materials used during the manufacture of tannate pharmaceutical compositions, such as those described in Chopdekar and Gordziel, versus that of the presently claimed composition, which use the method recited in claims 1, 31, and 53. In particular, the content variation for the common salt of pyrilamine is 2.50%, whereas the content variation range for the tannate salt of pyrilamine is 6%. And the content variation range for the common salt of phenylephrine is 5%, whereas the content variation range for the tannate salt of phenylephrine is 9%. In each case, there is more variation in the active ingredient added to the formulation as tannate salt and processed into finished pharmaceutical compositions, such as those set forth in Chopdekar and Gordziel. The decrease in active ingredient variability

inherent in the claimed compositions due to the use of the method recited in the claims would be 3.50% for pyrilamine and 4% for phenylephrine. In the manufacture of pharmaceutical products, Applicants submit that these are very significant reductions in content variability. (*See* Declaration of H. Greg Thomas, paragraphs 9 and 10.)

Thus, in order for the compositions of Chopdekar and Gordziel to achieve the same level of active ingredient content uniformity as would be exhibited by the presently claimed composition, a correction in the amount added to the formulation must be made each time a batch is prepared using a different lot of tannate salt raw material. In fact, such a correction must be performed if the finished composition is to meet current international pharmaceutical product standards of 95%-105% of the target active ingredient amount. Failure to do so may result in a subpotent and unmarketable product. The necessity of performing such a calculation decreases the efficiency of the manufacturing process and introduces another possible source of error. (*See* Declaration of H. Greg Thomas, paragraph 11.)

The general cause of increased content variability that is inherently produced using the prior art methods of Gordziel and Chopdekar is not difficult to explain. Each step or operation performed in a manufacturing environment introduces some level of variability into the finished product. When the operation in question, such as a method of Gordziel and/or Chopdekar, involves isolating a tannate salt, such as by beginning with the free-base form and then converting to the tannate salt, and thereafter

processing those tannate salts into a composition, the variability is focused on the amount of active ingredient contained in the finished pharmaceutical product. By eliminating the additional isolation step required by the prior art that is a potential source of increased content variability, the compositions presently claimed by the Kiel process are able to provide a consistently better finished product. (*See* Declaration of H. Greg Thomas, paragraph 12.)

The decreased content variability that results in the claimed compositions due to the recited method has many real world advantages. A better finished in the pharmaceutical industry means a safer drug. The principal properties affected by converting a drug to the tannate salt form is solubility, which normally decreases after conversion to a tannate from a hydrochloride salt or bromide salt. The decreased solubility attained in this matter gives the drug prolonged action characteristics. Changes in the content of the tannate salt in a final drug product can potentially alter the overall amount of drug taken, as well as the rate at which the drug enters the body. Understandably, then, increased variability in drug content leads to increased risk to the patient taking the drug product. The need for increased safety and content uniformity is multiplied by the fact that many of the tannate drug products are designed for use by children. (*See* Declaration of H. Greg Thomas, paragraph 13.)

Applicants submit that since this general uniformity is generated by the particular process of the claimed invention, the differing steps of the present process

over that of the prior art provide for differences in the compositions that are formed by the respective processes: namely, that each dosage unit formed includes amounts of active pharmaceutical ingredients that are generally uniform when compared to all other dosage units formed. Applicants further assert that since neither Gordziel nor Chopdekar disclose the process steps necessary to generate such general uniformity of active pharmaceutical ingredients, the compositions produced in Gordziel and Chopdekar do not exhibit such general uniformity. Thus, in the present invention, the method changes the product over that found in the cited art. As a result, Applicants submit that, based on the method, the claimed product is patentable over the cited art.

Applicants note that neither Chopdekar nor Gordziel discloses the process by which the general uniformity of active pharmaceutical ingredient in the present composition is achieved. In fact, as previously noted, both Chopdekar and Gordziel describe the "old" routes of preparation, which Applicants describe in the application as forming compositions which vary in the amount of active pharmaceutical ingredient from dosage unit to dosage unit. Thus, Applicants submit that the composition disclosed in Gordziel or Chopdekar will not exhibit such general uniformity, and rather disclose compositions that exhibit variable levels of active pharmaceutical ingredient from dosage unit to dosage unit of the composition. As a result, Applicants submit that it cannot be the case that the composition disclosed in Gordziel is the same as the composition claimed in the present application. Applicants further submit that a

combination of Gordziel with Chopdekar also cannot render such a composition obvious, since Chopdekar also does not describe the process used to achieve the general uniformity of the amounts of active pharmaceutical ingredients, and thus does not disclose a composition exhibiting such general uniformity. (As noted above, Chopdekar itself says the dosages of its product may need to be adjusted; no such adjustment is necessary due to the homogeneity of the present product, which is specifically recited in the present claims,) Thus, Applicants assert that any combination of Gordziel and Chopdekar fails to teach every element of the invention as presently claimed.

In view of the above, Applicants assert that the combination of the Gordziel and Chopdekar references do not teach all the limitations of independent claims 1, 31, and 53 as presently amended, and further assert that the process of the independent claims renders a different product than that of Gordziel and Chopdekar. As such, Applicants respectfully request a withdrawal of the rejection of claims 1-21, 31-48, and 53 under 35 U.S.C. § 103.

Claim Rejections Double Patenting

Claims 1-21, 31-48, and 53 have been provisionally rejected under the judicially created doctrine of double patenting over claims 1-21, 31-48, and 53 of copending Application No. 10/645,977. In view of the claims as presently amended, Applicants respectfully disagree.

Applicants first note that each independent claim 1, 31, and 53 recite active pharmaceutical ingredients consisting essentially of phenylephrine and pyrilamine. The claims of copending application10/546,977 recite active pharmaceutical ingredients consisting essentially of phenylephrine, pyrilamine, and dextromethorphan. Applicants submit that the presently claimed composition is not obvious from that of the '977 application because the claimed compositions in each are materially different. Each of the actives recited in the claims of the copending '977 application have a specific purpose (e.g., as an antihistamine, antitussive, or decongestant). The removal of any ingredient materially changes the composition in that there is no longer a specific effect of the composition. Applicants therefore respectfully request a withdrawal of the rejection of claims 1-21, 31-48 and 53 under the judicially created doctrine of double patenting.

Conclusion

For the foregoing reasons, it is submitted that all claims are patentable, and a Notice of Allowance is respectfully requested.

Please consider this paper a Petition for an Extension of Time of three months, and apply the appropriate Extension of Time fee under 37 CFR 1.17(a)(2) to Deposit Account 23-3000. Any deficiencies or credits necessary to complete this communication should be applied to Deposit Account No. 23-3000.

The Examiner is invited to contact the undersigned attorney with any questions or remaining issues.

Respectfully submitted,
WOOD, HERRON & EVANS, L.L.P.

By: /David E. Jefferies/
David E. Jefferies, Reg. No. 46,800